201-14390

NCIC HPV
Sent by: Mary-Beth Weaver

04/09/2003 09:35 AM

To: NCIC HPV@EPA, Peter Wendolkowski/DC/USEPA/US@EPA
cc: Mary-Beth Weaver/DC/USEPA/US@EPA, Ralph Northrop/DC/USEPA/US@EPA, Vanessa Williams/DC/USEPA/US@EPA
cc: Mary-Beth Weaver/DC/USEPA/US@EPA, Ralph Northrop/DC/USEPA/US@EPA, Vanessa Williams/DC/USEPA/US@EPA
Subject: HPV Submission: 4-Nitrophenol

"Johannsen, Frederick R" <frjoha@solutia.com> on 10/31/2002 05:07:50 PM

To: Rtk Chem/DC/USEPA/US@EPA
cc:
Subject: HPV Submission: 4-Nitrophenol

Please see attached submission

<<HPVPNPtrans.doc>> <<HPV FinalP-NITROPHENOL.doc>>
<<pnp.rtf>>

- HPVPNPtrans.doc
- HPV FinalP-NITROPHENOL.doc
- pnp.rtf

Solutia Inc.
575 Maryville Centre Drive
St. Louis, MO 63141

P.O. Box 66760
St. Louis, MO 63166-6760

October 31, 2002

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

In re: HPV Challenge Program
AR-201
4-Nitrophenol
CAS Number 100-02-7

Solutia, Inc., Company Registration Number , is pleased to submit the attached Test Plan and Robust Summaries for 4-nitrophenol (CAS Number 100-02-7) as a part of our commitment to the EPA High Production Volume Challenge Program (AR-201).

The attached files are:

1. This cover letter in MS Word 2000
2. Test Plan in MS Word 2000
3. Robust Summaries (IUCLID format) in MS Word 2000

The complete matrix of SIDS data elements, including physical/chemical properties and results of biological and toxicology studies, indicate that no additional testing is required.

Please contact me at 314-674-8815 if there are any questions relating to this submission.

Sincerely,

Frederick R. Johannsen

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

4-NITROPHENOL

CAS NO. 100-02-7

Prepared by:

Solutia, Inc. Registration No.

575 Maryville Centre Drive,
St. Louis, Missouri 63141

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EXECUTIVE SUMMARY

Solutia Inc. voluntarily submits the following screening information data and Test Plan covering the chemical, 4-Nitrophenol, also known as para-Nitrophenol or PNP (CAS No. 100-02-7), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with PNP. Use of key studies or estimation models available from data already developed provide adequate support to characterize each Endpoint in the HPV Chemicals Challenge Program without the need for additional, unnecessary testing.

TABLE OF CONTENTS

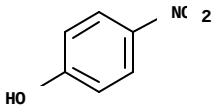
TEST PLAN FOR P-NITROPHENOL (PNP)

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on Phenol, 4-nitro-, or PNP. The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of PNP, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed on behalf of Solutia Inc. or found in the published scientific literature and fulfills Solutia's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of PNP and associated nomenclature.



Phenol, 4-nitro-

CAS No. 100-02-7
Synonyms: 4-Hydroxynitrobenzene; p-Nitrophenol; para-nitrophenol; PNP

B. Manufacturing & Use

PNP is manufactured by a single US producer, Solutia Inc., at a single manufacturing site. The manufacturing operation is a closed, continuous process. Only a few employees are involved in its manufacture and have minimal potential for skin or airborne exposure, which occur chiefly during material transfer operations. Due to the high acute hazards associated with its potential to cause methemoglobinemia, specific manufacturing procedures and practices have been established to minimize the exposure potential to PNP.

p-Nitrophenol is sold to a limited number of customers at a few US processing sites and exported to ex-US sites for the express purpose of full chemical conversion into other

industrial chemicals. As such, PNP is expected to chemically react to form chemicals used as dyes/pigments, pharmaceuticals, analgesics and adhesives. There are no known or suspected consumer exposures to PNP resulting from TSCA-related activities, as PNP is consumed as a chemical intermediate. Loss to the atmosphere or from non-POTW aqueous streams during manufacturing or processing is minimal. Hence, very limited occupational or environmental exposure is expected to occur.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or 3) were estimated using environmental models accepted by the US EPA (1999b) for such purposes. This initial assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with PNP. The data used to support this program include those Endpoints identified by the US EPA (1998a); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VI. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,

2. Reliable with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3.Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – This designation not used in this Dossier.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. Additional studies have been identified during our literature search on the referenced HPV endpoints but have not been summarized in this Dossier. The reader is referred to three additional data compendia which also summarize available data on the physical-chemical properties, ecotoxicity, environmental fate and health effects of p-nitrophenol. These include the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000), the ECB IUCLID Dossier for p-Nitrophenol (2002), and the Hazardous Substances Data Bank (HSDB) (2002) for p-Nitrophenol.

II. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: All HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. Hence, no further testing for any of the HPV Endpoints is deemed necessary (Table 1).

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were obtained from reputable references and cited as an Accepted or Peer Reviewed value in the PNP Hazardous Substances Data Bank (2002) and/or IPCS CICAD on Mononitrophenols (2000). These endpoints have been classified as "2-Reliable with restrictions".

Environmental Fate values for Transport (Fugacity) were obtained using a computer estimation –modeling program (EPIWIN, 2002) recommended by EPA; they have been classified as "2-Reliable with restrictions". Biodegradation data were summarized in a published article reporting results of multiple studies following OECD # 301/GLP guidance and thus classified as "1-Reliable without restriction". Photodegradation data was obtained from a published study following EPA test guidelines and was considered "2-Reliable with restrictions". In keeping with OECD SIDS guidance, no testing for Stability in Water is planned with PNP as it is generally recognized as "stable" in aqueous solutions.

Ecotoxicity Endpoints were met with studies that were conducted according to OECD guidelines for Acute Invertebrate Toxicity (OECD 202) and Acute Plant Toxicity (OECD 201), or conducted according to study design and test parameters which preceded, but were consistent with OECD test guidance (Acute Fish Toxicity-OECD # 203). Studies supporting the Acute Invertebrate and Acute Plant Endpoints were designated a reliability level of "1-Reliable without restriction", while the Acute Fish study was designated "2-Reliable with restrictions", as it was well documented but conducted prior to inception of GLPs.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing, and Reproductive Toxicity) have all been filled by way of tests which either conformed directly with OECD test guidance or followed test designs similar to OECD guidance. The Acute Toxicity Endpoint was supported by a study which followed OECD guideline 401 and GLPs and was considered "1- Reliable without restriction". The Repeated Dose Toxicity Endpoint was met with an OECD guideline 408 study conducted in accordance with GLPs. It also was codified as "1- Reliable without restriction". Both the Ames test as well as an *in vitro* Chromosomal Aberration assay, used to support their respective Endpoints, were conducted by the US National Toxicology Program (NTP). The Ames test followed a study design equivalent to OECD guideline # 471 while the cytogenetics study was similar to, but not identical with, OECD guideline # 473. Thus, the Ames test was categorized as "1- Reliable without restriction" while the cytogenetics study was classified as "2- Reliable with restrictions".

A 2-Generation Reproduction Study fulfills the HPV requirements for the last Mammalian Toxicity Endpoint. This study was conducted to meet US EPA pesticide guidance for reproductive toxicity both in design and GLP compliance. While it deviated slightly from OECD guideline # 416, it has been classified as "1- Reliable without restriction" since it has been accepted by EPA to fulfill the Reproductive Toxicity data requirement for reregistration purposes.

Following is a tabular depiction of data availability and testing recommendations for p-Nitrophenol (PNP).

Table 1. Test Plan Matrix for para-Nitrophenol

	Info. Avail.?	OECD?	GLP?	Other Study?	Estimat. Method?	Accept-Able ?	Testing Recomm.?
PHYSICAL CHEMICAL							
Melting Point	Y	R	N	Y	-	Y	N
Boiling Point	Y	R	N	Y	-	Y	N
Vapor Pressure	Y	R	N	Y	-	Y	N
Partition Coefficient	Y	R	N	Y	-	Y	N
Water Solubility	Y	R	N	Y	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	L	Y	-	Y	N
Stability in Water	Y	N	N	N	-	Y	N
Biodegradation	Y	Y	L	Y	-	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	N	Y	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	N	Y	-	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	L	Y	-	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	L	Y	-	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	Y	Y	Y	-	Y	N
Repeated Dose Toxicity	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	N	Y	Y	-	Y	N
Reproductive Toxicity	Y	N	Y	N	-	Y	N

Y = Yes; N = No; L = Likely, but not specified; R = Reputable Reference;
- = Not applicable

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VI of this dossier.

A. Chemical/Physical Properties

Table 2. Selected Chemical/Physical Properties of para-Nitrophenol (PNP)

Chemical	Boiling Pt. (^{o}C.)	Melting Pt.(^{o} C.)	Vapor Pressure (hPa @ 20 ^{o}C)	Water Solubility (mg/L)	Partition Coefficient (Log Kow)
p-Nitrophenol CAS No. 100-02-7	> 279	114	0.0067	16,000 @ 25 ^{o}C.	1.91

All HPV Endpoints for Chemical/Physical Properties have been completed with reliable information and taken from either primary or reputable textbook references (Table 2). The values, which are included in the Robust Summary section of this Dossier, have been internationally accepted as accurately depicting the properties of PNP and are cited in the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000) and/or cited as peer-reviewed references in the Hazardous Substances Data Bank (HSDB, 2002). They have been classified as "2-Reliable with restrictions". Additional Chemical/Physical property values can also be found in the IPCS CICAD No. 20 (2000) and the ECB IUCLID Dossier for P-Nitrophenol (2002).

In summary, these data indicate that PNP is a solid at room temperature and has a low vapor pressure. It has a low octanol:water partition coefficient and is soluble in water.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

Extensive reviews and study citations in the Environmental studies area have been published on PNP, and are summarized in the IPCS CICAD (2000), in the HSDB (2002) and in the ECB IUCLID Dossier (2002) for PNP. Key studies have been selected for this

Dossier, which fairly depict the consensus conclusion/values for each of the HPV Endpoints listed (Table 3), and are summarized in the Robust Summary section of this Dossier. A comparative assessment of PNP Biodegradability employing 5 OECD Guideline 301 methods fulfills this HPV Endpoint; it has been designated as "1-Reliable without restriction". The molecular structure of PNP possesses only 2 functional groups (aromatic nitro and phenol), both of which are listed as types of Organic Functional Groups that are Generally Resistant to Hydrolysis (Table 7.1, Lyman et al, 1990). PNP is also considered "stable" in water by the German Umweltbundesamt, based on tests conducted in Germany (Schmidt-Bleek et al, 1982). PNP hydrolysis has also been reported as "nil" at pH 2, pH 7 and pH 12 (Capel and Larson, 1995). Photochemical degradation of PNP in an aquatic system has been evaluated in "the EPA Test" using the methodology of Leifer and Stern (Hustert et al, 1981). Estimation of Transport (Fugacity) was made using an EPA-accepted estimation model (EPIWIN, 2002). These values have been designated as "2-Reliable with restrictions". An overview of the known qualities of the environmental properties of PNP is provided below.

The Environmental Fate of PNP can be summarized, as follows. Upon release to the air, PNP would be expected to exist in a vapor state, based on its vapor pressure and would be degraded in the atmosphere by reaction with photo chemically-produced hydroxyl radicals; the half-life for this reaction in air is approximately 6 days (Table 3 - Photodegradation). However, PNP is extensively adsorbed to particles, in both the air and soil. Thus, as PNP is mostly particle-bound, its availability for photochemical reactions is limited (IPCS, 2000). Significant volatilization from soil or water to air is not expected, based on its Vapor Pressure (Table 2) and Henry's Law constant, respectively (IPCS, 2000). Atmospheric PNP, bound to particles, is expected to wash out to surface waters and soils by dry and wet deposition. Fugacity modeling (Table 3) indicates virtually complete allocation to water and soil; essentially no allocation was made to air or sediment (Table 3 - Fugacity). In aqueous solution, PNP appears stable (Table 3-Stability in Water). PNP has been classified as possessing low to moderate potential for soil sorption and can be decomposed under aerobic conditions, thus being classified as "Inherently Biodegradable" (IPCS, 2000)(Biodegradation – Table 3). Microbial decomposition can occur in different environmental compartments after adaptation of the microflora. Further biotic degradation under anaerobic conditions also occurs following extended acclimatization of microbial communities (Table 3 - Biodegradation). Measured values (IPCS, 2000; ECB IUCLID, 2002) indicate PNP has a low potential for bioaccumulation in aquatic species.

Table 3. Environmental Fate and Biodegradation Parameters for para-Nitrophenol (PNP)

Chemical	Biodegradation Rate	Stability in Water	Fugacity (%)	Photodegrad. Rate (T ½)
p-Nitrophenol CAS No. 100-02-7	~ 90 %	Stable	Air – 4.98 Water – 36.3 Soil – 58.7 Sediment – 0.02	5.7 (pH 5) 6.7 (pH 7) 13.7 (pH 9) .

Conclusion – Adequate studies following either OECD or EPA test guidance are available to provide needed information regarding the Biodegradation and Photodegradation of PNP. Information on Transport (Fugacity) were completed using EPIWIN, an accepted estimation-modeling program. As PNP possesses only functional groups generally known to be resistant to hydrolysis, testing for stability in water is not needed (SIDS Manual-new draft version). Therefore, no additional data development is warranted for these HPV Endpoints.

C. Aquatic Toxicity

The aquatic toxicity of PNP has been extensively reviewed (IPCS, 2000; HSDB, 2002; ECB IUCLID, 2002) and contains both acute and chronic toxicity studies on algae, invertebrates and fish. Studies selected for development of Robust Summaries are reported in Table 4 and depict the level of toxicity generally observed for these Endpoints within the overall dataset.

Both the Acute Invertebrate and the Acute Algae studies were conducted according to OECD test guidance # 202 and 201, respectively. While no mention was made of GLP compliance in the referenced publications, it is reasonable to assume both were conducted under GLP auspices as they followed OECD method guidance and were conducted to meet national regulatory mandates. Thus, both studies are considered "1-Reliable without restriction". The Acute Fish Toxicity study was conducted prior to inception of OECD/GLP guidance but is considered well documented and used methodology consistent with OECD guidance for this study type. This study is considered "2- Reliable with restrictions" only because it was conducted prior to codification of testing and GLP guidelines.

Table 4. Aquatic toxicity parameters for para-Nitrophenol (PNP)

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
p-Nitrophenol CAS No. 100-02-7	5.8 (bluegill-96 hr)	22.0 (Daphnia-48 hr)	32.0 (96-hrs)

PNP is considered to be "Slightly Toxic" toward these and other aquatic species following acute testing (IPCS, 2000). Based on the pattern and release scenarios envisioned, PNP is expected to present a negligible risk to aquatic organisms.

Conclusion – Adequate studies which meet internationally accepted test guidelines are available on all 3 Aquatic Toxicity Endpoints to assess the acute aquatic toxic hazards associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 5. Each report has been further summarized in the Robust Summary section of this Dossier.

Table 5. Mammalian Toxicity of p-Nitrophenol (PNP)

Chemical Name/ CAS no.	Acute Toxicity		Repeat Dose Toxicity			Reprotoxicity	Mutagenicity –In Vitro	
	OLD50 (rat)	DLD50 (rabbit)	90-day	28-day	Chronic	2-Gen.	Ames	Chrom. Aberr.
p-Nitro-phenol 100-02-7	230 mg/kg	> 5000 mg/kg	(oral-rat) NOEL 25 mg/kg/d	(inhal-rat) NOEL 5 mg/m3	(dermal-mouse) NOEL (systemic tox./carcin.) 160 mg/kg/d	(dermal-rat) NOEL (maternal-systemic) 250 mg/kg/d NOEL (reprotox) 250 mg/kg/d	Neg.- All strains +/- S9	Neg. (- S9) Pos. (+S9)

1.0 Acute Toxicity

Results of acute toxicity studies by both the oral and dermal routes of exposure have been conducted as summarized in Table 5. Both studies were conducted using study designs consistent with OECD Test Guidelines 401 and 402, respectively, under auspices of GLPs, and are deemed "1- Reliable without restriction". The acute rat oral toxicity study has been chosen as the key study to fulfill this HPV Endpoint. The acute rabbit dermal toxicity study is included as Supplemental information.

PNP is considered to be moderately toxic after acute oral exposure to rats. As there were no deaths or untoward signs of toxicity after acute dermal exposure well above generally accepted Limit Dose levels (1,000 mg/kg), PNP is considered practically non-toxic after acute dermal exposure to rabbits. However, based on the ability of PNP to produce methemoglobinemia in humans, this material is considered to be toxic in the workplace by all acute exposure routes. Additional acute toxicity values in animals can be found listed in the three compendium reports cited above.

Conclusion – A quality study, compliant with OECD/GLP guidance, is available to assess the Acute hazards associated with PNP. Therefore, no additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

PNP has been adequately tested by several routes of exposure to define its Repeated Dose Toxicity. The key study used for this HPV assessment is cited in Table 5 and summarizes a 90-day subchronic rat study by the oral route. This study was conducted using a study design consistent with OECD Test Guideline 408, and under GLP auspices and is considered "1- Reliable without restriction". Early deaths related to PNP acute toxicity, and exacerbated by repeat dosing, occurred at dosage levels of 70 and 140 mg/kg/d. No other treatment-specific effects or organ pathology, including lack of involvement of male and female gonads (i.e. testes and ovaries), were affected. A NOEL of 25 mg/kg/d was established. A summary of this study and a 4-week Range Find study are found in the Robust Summary section of this Dossier. The IPCS CICAD (2000) also summarizes a 28-day oral gavage study (Andrae et al. 1981) with PNP at substantively higher levels, which resulted in excessive toxicity. This study was not considered in this review as it is not available in English and is superceded by the current study, which is of a longer exposure duration by the same route and has utilized a more appropriate selection of doses.

PNP also has been tested following inhalation exposure (Table 5). This study was not selected for inclusion as the key Repeated Dose Study, as it was conducted for a shorter (4-weeks) time period than the 90-day study referenced above. However, it too is considered "1- Reliable without restriction" and is included in the Robust Summary section of this Dossier.

It should be noted that no evidence of effects on the gonads was seen in either sex of rat in the studies cited above. Further, results of an 18-month chronic toxicity study in male and female mice (NTP, 1994) also cited in Table 5, resulted in no organ-related toxicity, including the gonads, up to the highest level tested (160 mg/kg/d, 3x/wk, 78 wks).

Conclusion - Thus, the Repeated Dose HPV Endpoint for PNP has been fulfilled with a 90-Day Subchronic study in rats deemed "1- Reliable without restriction". No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Mutagenicity and Chromosomal Aberrations

3.1 Mutagenicity Testing (Ames test)

PNP has been extensively tested in the standard Ames assay for point mutations (ECB IUCLID, 2002; IPCS CICAD, 2000). PNP elicited no mutagenic response in any of the *S. Typhimurium* tester strains employed, either with or without inclusion of metabolic activation. The Haworth et al, (1983) study, conducted on behalf of the NCI/NTP program, has been summarized in the Robust Summary section of this Dossier and its results are referenced in Table 5. Its design and documentation are such that it is considered equivalent to OECD guideline # 471 and thus is "1- Reliable without restriction" for this assessment. Additionally, PNP has been tested in the secondary tier *Drosophila* Sex-Linked Recessive Lethal assay; no mutagenicity was observed after either oral or injection dosing up to lethal doses by each route in this same NCI/NTP program (NTP, 1994). Oberly et al, 1990 reported that PNP elicited no mutagenic activity when tested in a CHO-HGPRT forward mutation assay in mammalian cells.

Thus, it is concluded that adequate testing of sufficient quality has been performed on PNP to evaluate the Ames Test (Point Mutation) HPV Endpoint; no further testing is needed for this Endpoint.

3.2 - Chromosomal Aberrations

As part of the NCI/NTP program (Galloway et al 1987), PNP was tested in the CHO cell *in vitro* assay to determine its capacity to induce chromosomal aberrations. A Robust Summary has been prepared for this study and its results are referenced in Table 5. PNP was negative for structural chromosome damage up to severely cytotoxic concentrations (>750 ug/ml) in a metabolic activation system-free environment. It did produce reproducible, dose-related and statistically significant increases in cells with structural chromosomal aberrations at levels of 1500 and 1700 ug/ml PNP after metabolic activation, although cells at these levels had undergone severe cell cycle delay. The quality of this study is considered to be "2- Reliable with restrictions", as it did not follow an established OECD protocol, yet was well documented and has been used for regulatory purposes. In a corresponding Sister Chromatid Exchange (SCE) assay

conducted in the same CHO cell test (Galloway et al. 1987), PNP produced no SCEs up to doses that caused severe cell cycle delay (25 ug/ml without S9 and 1700 ug/ml with S9).

The HPV Chromosomal Aberration Endpoint for testing of PNP has been fulfilled with adequately conducted and documented studies and no further testing is needed.

4.0 Reproductive Toxicity

A Two-Generation rat Reproduction Toxicity study of dermally applied PNP has been conducted (Table 5) and summarized in Dossier section VI - Robust Summaries. This study is considered adequate for assessment of this Endpoint as it has been accepted as such by IPCS (2000) and was judged "adequate" for US EPA pesticide reregistration (US EPA, 1998b). It was conducted under GLPs and followed OPPTS testing guidelines. Based on general acknowledgement of its scientific and regulatory acceptability, it has been judged as "1- Reliable without restriction" for purposes of this assessment. PNP was administered dermally in ethanol to groups of 12 male and 24 female rats at 50, 100 and 250 mg/kg/d. No indication of systemic toxicity was observed in either parental generation, although dermal irritation was observed at the site of application. No reproductive toxicity was observed at any dose tested in either the F1 or F2 matings. Both the adult systemic and reproductive toxicity NOELs are considered to be the highest dosage tested, i.e. 250 mg/kg/d.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled with conduct of a Two-generation rat study which followed regulatory testing guidance, was conducted under GLPs, and accepted in support of pesticide reregistration. Thus, no further testing for this HPV Endpoint is required.

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VI. ROBUST STUDY SUMMARIES -

IUCLID Data Sets are appended

I U C L I D

Data Set

Existing Chemical	:	ID: 100-02-7
CAS No.	:	100-02-7
EINECS Name	:	4-nitrophenol
EINECS No.	:	202-811-7
TSCA Name	:	Phenol, 4-nitro-
Molecular Formula	:	C6H5NO3

Producer Related Part

Company	:	Solutia Inc.
Creation date	:	04.04.2002

Substance Related Part

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1.0.1 OECD AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

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1.6.2 CLASSIFICATION

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1.7.1 TECHNOLOGY PRODUCTION/USE

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1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

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1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

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1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= 114 ° C
Sublimation	:	
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol; also cited as a definitive value in IPCS CICAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (2)

2.2 BOILING POINT

Value	:	> 279 ° C at
Decomposition	:	
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as Peer reviewed reference in HSDB (2002) for 4-nitrophenol; Cited as definitive value in IPCS CICAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (19)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .0067 hPa at 20° C
Decomposition	:	
Method		other (calculated)
Year	:	1988
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as Peer reviewed reference in HSDB (2002) for 4-nitrophenol.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (11)

2.5 PARTITION COEFFICIENT

Log pow	:	<= 1.91 at ° C
Method		other (calculated)

Year	:	1985
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Value of <2.4 cited as definitive value in IPCS CIDAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (7)

2.6.1 WATER SOLUBILITY

Value	:	= 16000 mg/l at 25 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (18)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	other		
Light source	:			
Light spect.	:	nm		
Rel. intensity	:	based on Intensity of Sunlight		
Spectr. of subst.	:	lambda (max, >295nm)	:	290 nm
		epsilon (max)	:	
		epsilon (295)	:	
Conc. of subst.	:	10 mol/l at degree C		
Direct photolysis				
Halflife t1/2	:	= 5 - 7 day		
Degradation	:	% after		
Quantum yield	:			
Deg. Product	:			
Method	:	other (measured)		
Year	:	2002		
GLP	:	no data		
Test substance	:	no data		
Method	:	Dissolved in deionized water (1.18 g/100 ml) to which was added an acetate, phosphate or borate component to bring solution to pH 5, 7 or 9, respectively and introduced to sunlight (blind controls used). Analysis performed by GC using EC detector.		
Result	:	Half-life of 5.7 days at pH of 5, 6.7 days at pH of 7 and 13.7 days at pH 9.		
Reliability	:	(2) valid with restrictions Matches well vs. estimated value based on accepted model, ie AOP EPIWIN which estimated degradation to be 2.48 days, based on 12-hr day and 1.5e6 OH/cm3.		
Flag	:	Critical study for SIDS endpoint		

24.10.2002 (9)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other
Air (level I)	:	4.98
Water (level I)	:	36.3
Soil (level I)	:	58.7
Biota (level II / III)	:	
Soil (level II / III)	:	.0147
Method	:	other
Year	:	2002
Method	:	Level III Fugacity Model; EPIWIN:RQC from Syracuse Research Corp.; Physical chemical values utilized in this model were user entry measured values (mol wt=139.11; Henry's LC=1.3e-008 atm-m3/mole (user entered); Vapor Press=0.005 mm Hg (user entered); Log Kow=1.91 (user entered); Soil Koc=33.3 (calc. by model) obtained from reference sources. Emissions rates were 1000 kg/hr for each of the three main compartments, air, water

rates were 1000 kg/hr for each of the three main compartments, air, water and soil.

```
Level III Fugacity Model (Full-Output):
=======================================
  Chem Name   : p-Nitrophenol
  Molecular Wt: 139.11
  Henry's LC  : 1.3e-008 atm-m3/mole (user-entered)
  Vapor Press : 0.005 mm Hg  (user-entered)
  Log Kow     : 1.91  (user-entered)
  Soil Koc    : 33.3  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       4.98            19           1000
   Water     36.3            20           1000
   Soil      58.7            20           1000
   Sediment  0.0147          60           0

              Fugacity    Reaction    Advection   Reaction
Advection
               (atm)      (kg/hr)      (kg/hr)    (percent)
(percent)
   Air       7.37e-012    153         42          5.1
1.4
   Water     1.43e-014    1.06e+003   30.6        35.4
1.02
   Soil      2.33e-013    1.71e+003   0           57.1
0
   Sediment  1.61e-015    0.143       0.000248    0.00477
8.27e-006

   Persistence Time: 28.1 hr
   Reaction Time:    28.8 hr
   Advection Time:   1.16e+003 hr
   Percent Reacted:  97.6
   Percent Advected: 2.42

   Half-Lives (hr), (estimated from experimental data):
      Air:      19
      Water:    20
      Soil:     20
      Sediment: 60

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004
```

Reliability : (2) valid with restrictions
Estimated value based on accepted model. Second soil value was for sediment.

Flag : Critical study for SIDS endpoint

24.10.2002 (3)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum :

Contact time	:	
Degradation	:	1 - 100 % after 10 day
Result	:	other
Deg. Product	:	
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	no data
Method	:	Report contains a comparative assessment of a series of Biodegradabiltiy studies all performed in accord with OECD Guideline 301. Studies included: Coupled Units test, Zahn-Wellens test, MITI test, AFNOR test, Sturm test, OECD Screen test and Closed bottle test.
Result	:	With the exception of the Closed bottle test and the MITI test, which yielded low results, PNP was considered sufficient or even readily biodegradable in all other tests conducted. The degree (% DOC removed) for each test (days to complete) was: Coupled Units test - 100+/-4 % (7d); Zahn-Wellens test - 92%(10d); MITI test - 1%; French ANFOR test - 97%; Sturm test - 97%; and Closed bottle test - 60% (30d).
Test substance	:	No data cited in article, but typical technical grade PNP has purity of 99% and was likely used in these studies.
Reliability	:	(1) valid without restriction Use of OECD methodology acceptable for regulatory review and decision-making.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (5)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	c >= 5.8
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	other TS
Method	:	This study preceeded development of OECD Test Guideline 203 but was conducted in a manner consistent with that guideline. Groups of bluegill fingerlings (mean length of 2.8 cm); fish were not fed 48 h prior to nor during the 96 hr exposure period. Groups of 10 fish were added to glass vessels containing 15 l water at 5 test concentrations (8.7, 5.6, 3.7, 2.4 and 1.6 mg/L PNP dissolved in acetone. Both a negative control and an acetone-containing control group were also used. No aeration was performed during the test. Water temperature was maintained at 22+/-1%, with a pH ranging between 6.7-6.3. Dissolved oxygen ranged from 93% saturation at study start to 7% at study termination. Observations and mortality were checked every 24 hr. At the end of the study, test concentrations and observed mortality were converted to logarithms and probits, respectively, and analyzed by a least square regression method for determination of LC50 and CI at 24, 48, and 96 hr timepoints.
Result	:	All deaths occurred during the first 24 hr of the study, hence the LC50 and CI values for each of the study time points (24, 48, 96 hr) were the same, i.e. LC50 = 5.8 (3.7-9.2) mg/L. Mortality (%) observed at each PNP concentration was: 100% @ 8.7 mg/L, 10% @ 5.6 mg/L, and 0% @ 3.7 mg/L, 2.4 mg/L, 1.6 mg/L, untreated control and acetone control.
Test substance	:	Purity of 99%.
Reliability	:	(2) valid with restrictions This study was conducted prior to, but consistent with OECD Guideline # 203 and, US GLP guidelines effective in 1979 for nonclinical laboratory studies.Reduction in oxygen over time is not considered a factor in interpretation of results since all deaths (10%) occurred within first 24 hrs of study.
Flag	:	Critical study for SIDS endpoint

09.10.2002 (12)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	m >= 13
EC50	:	c >= 22
Method	:	OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year	:	1980
GLP	:	no data
Test substance	:	other TS
Method	:	Methods used followed protocol as found in US EPA,1975 for Macroinvertebrate testing, which are consistent with OECD Guideline 202. D. magna, <24h old, were used as the tester strain. Culture water was reconstituted as outlined in US EPA, 1975 guidance, such that it contained

reconstituted as outlined in US EPA, 1975 guidance, such that it contained a total hardness of 173+/-13 mg/l as CaCO3 and a pH of 8.0+/-0.2. Temperature was maintained at 22+/-1 degree C. A stock solution of the chemical in distilled water was prepared and used to provide a series of graded concentrations (reportedly 5-8) for testing. PNP was added to 500 mL diluent water in 2-L jars to prepare for each test solution. The 500 mL volume of test solution was divided into three 150-mL aliquots to provide triplicate exposures at each concentration. Five Daphnids were randomly placed in each test solution within 30 min of preparation. A negative control was also tested. Meaurements were taken to confirm dissolved oxygen concentration, pH, and temperature in the high, medium and low test concentrations. Observations were made at 24 and 48 hours of exposure and any mortalities were recorded. Mortality data were used to calculate an LC50 and CI using a moving average angle method.

Result : LC50 (CI) values for 24 hr and 48 hrs were, respectively, 24 (22-26) mg/L and 22 (20-24) mg/L. ; The No Discernable Effect level was 13 mg/L. Dissolved oxygen concentrations ranged from 6.5-9.1 mg/L, pH values measured 7.4-9.4 units.

Test substance : Test compound purchased from commercial chemical supplier, hence technical grade PNP was likely used and had purity of 99%.

Reliability : (1) valid without restriction GLP compliance was not stated in the article but adequate documentation can be assumed as this study was performed for the US EPA under contract no. 68-01-4646.

Flag : Critical study for SIDS endpoint

23.08.2002 (10)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Scenedesmus subspicatus (Algae)
Endpoint : growth rate
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : no
EC10 : c >= 8
EC50 : c >= 32
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1985
GLP : no data
Test substance : other TS

Method : Following test guidelines set by OECD, 1983 and German Umweltbundesamt, 1982. Experiments were incubated at 22+/-2 degrees C. at constant photosynthetically effective light intensity. Due to a distinct change of pH value caused by inclusion of PNP in sterilized double distilled water used as the diluent in this study, the pH of the stock solution was adjusted to pH 7 using NaOH. Experiments were performed by preparing two parallel dilution series in 300-ml Erlenmeyer flasks containing a saturated test chemical solution, medium and 5 ml algae suspension of approx. 10E4 cells/ml. Each Erlenmeyer flask was shaken 2-3 times per day and continuously illuminated from the side by two fluorescent lamps. After 0, 72 and 96 hrs, the cell growth of a 10-mm layer of cell suspensions from each test culture and from the controls was measured at 578 nm using a spectrophotometer. The extinction units were converted to cell numbers using a standard curve and the cell numbers determined using the Utermoehl method. The concentration-effect relationships were plotted on semilogarithmic paper and EC10 and EC50 values determined graphically.

Test substance : Commercial grade PNP, and thus with purity of 99%.

Reliability : (1) valid without restriction
While not explicitly stated, the fact that this study was conducted according

to national (Ger) and international (OECD) test guidelines it most likely was conducted consistent with or actually followed GLP guidance.

Flag : Critical study for SIDS endpoint
23.08.2002 (6)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	50
Vehicle	:	other
Value	:	= 230 mg/kg bw
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	Administered by gavage using propylene glycol as vehicle to 5 groups of rats (5 male and 5 female) given 70, 110, 171, 268 or 420 mg/kg/d; Clinical signs recorded 3X during first 8-hr after dosing and 2X daily for the remainder of the 14-d observation period. Body weights recorded on test days 0, 7 and 14. All survivors were necropsied on test day 15. Food and water administered ad libitum. LD50 and CI determined using method of Finney, DJ. 1971. Probit Analysis, Cambridge Univer. Press.
Result	:	LD50 +/- Confidence Limits (95%): 230 mg/kg (182-289 mg/kg); Deaths: 70 mg/kg (0/10), 110 mg/kg (0/10), 171 mg/kg (3/10), 268 mg/kg (8/10) and 420 mg/kg (8/10); Deaths all occurred within the first 8 hrs of dosing and exhibited the following clinical signs: convulsions, prostration and dyspnea prior to death; Clinical signs observed in survivors during the first three days after dosing included: tremors, ptosis, salivation and lethargy. No untoward effects were noted at necropsy of survivors.
Test substance	:	Technical grade purity of > 99%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

09.10.2002 (16)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10
Vehicle	:	physiol. saline
Value	:	> 5000 mg/kg bw
Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	One group of 5 male and 5 female rabbits were administered 5000 mg/kg/d test material on the shaved and abraded dermal surface. After administration the site was occluded and test material left in place for 24 hours. After test material removal, animals were observed for the remainder of the 14-d observation period. Clinical signs were recorded 3X during the first 8 hrs and 2X daily for the remainder of the study. Body weights were recorded on test days 0, 7 and 14. Necropsies were performed on all animals on test day 15. Food and water were administered ad libitum.

Result	:	No deaths occurred and no signs of systemic toxicity were seen during the study or at necropsy. Erythema and edema were observed during visual observations and at necropsy.
Test substance	:	Technical grade purity of > 99%
Reliability	:	(1) valid without restriction

09.10.2002 (17)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	13 weeks
Frequency of treatment	:	Once daily throughout the exposure period
Post obs. period	:	None
Doses	:	0, 25, 70 and 140 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL	:	>= 25 mg/kg
LOAEL	:	= 70 mg/kg
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	1989
GLP	:	yes
Test substance	:	other TS
Method	:	Groups of 20M and 20F S-D rats were administered 0, 25, 70 or 140 mg PNP/kg daily in distilled water for 13 weeks by gavage at a constant volume of 10 ml/kg. Dose levels were verified by spectrophotometric analysis. Mortality checks and signs of intoxication were made twice daily, and detailed clinical signs, individual body weights and food consumption recorded weekly. Pre and post study ophthalmoscopic examinations were also conducted on all animals available. At weeks 7 and 14 extensive hematology (RBC, RETIC, HGB, HCT, PLATELET, WBC, differential Leukocytes, and cell morphology) and serum chemistry (GLU, BUN, CREAT, AST, ALT, GGT, T PROT., ALBU, GLOB, CA, T BILI, PHOS, NA, POTAS, CL) parameters were conducted on blood samples from 10 animals/sex/group. No urinalysis was performed. At termination brain, liver, kidney, spleen and testes with epididymides were weighed for all survivors and a full necropsy performed. A full set of approx. 40 tissues and organs (including gonads) were collected from all surviving animals and sections were examined microscopically from these tissues for the control and high dose animals. Microscopic examination of tissues was also performed on tissues of premature deaths exhibiting gross autopsy findings. Temperature, lighting and humidity were controlled throughout the study. Body weights and weight gains, food consumption, hematology and clinical chemistry parameters and organ weights (absolute and relative) were initially analyzed using Levine's test of homogeneity of variances. If

initially analyzed using Levine's test of homogeneity of variances. If nonhomogeneous, data were transformed and then analyzed via ANOVA ($p<0.05$). Dunnett's t-test (2-tail, $p<0.05$) was used to compare treated and control groups. Cumulative survival was assessed using the National Cancer Institute statistical package and analyzed for trend.

Result : Early deaths were seen in groups of male and female rats given 70 and 140 mg/kg/d PNP. Total premature deaths observed in 0, 25, 70 and 140 mg/kg males were 0,0,1, 15, respectively; for females - 0,1,1,6, respectively; Several of these premature deaths (1-70 mg/kg male, 2 @ 140 mg/kg male, 3 @ 140 mg/kg female) died shortly after bleeding at wk 7, which likely exacerbated deaths, while 1 HD male was found to have died from gavage error. All other deaths at 70 mg/kg and 140 mg/kg were considered related to PNP exposure as they exhibited significant clinical signs of toxicity (pale appearance, languid behavior, prostration, wheezing and dyspnea), died shortly after dosing and exhibited moderate to severe congestive liver, kidney, lungs and adrenal cortex pathology (which correlated with necropsy findings) after microscopic examination; The presence of clinical signs of toxicity and absence of specific histopathological changes in these premature deaths suggests a relationship to acute pharmacologic/toxicologic effect. The single premature death observed in the LD female group was not considered treatment-related as there were no clinical signs observed, it did not die shortly after dosing (was found dead overnight) and had little in the way of organ congestion. Significant increases were observed in segmented neutrophils and absolute monocytes and eosinophil counts, as well as polychromasia of erythrocytes in 140 mg/kg animals of both sexes; these findings were considered of no toxicological significance. No treatment-related effects were observed in clinical signs, body weights, food consumption, ophthalmoscopic examination, organ weights or histopathology of survivors. Specifically, no effects were observed on gonads in this study. A NOEL was established as 25 mg/kg/d.

Test substance : Purity of 99%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.10.2002 (15)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 4 weeks
Frequency of treatment : 6 hr/d, 5 days/week
Post obs. period : none
Doses : 0, 1, 5, and 30 mg/m3
Control group : yes
NOAEL : >= 5 mg/m³
LOAEL : = 30 mg/m³
Method : OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
Year : 1984
GLP : yes
Test substance : other TS
Method : Groups of 15 male and 15 females S-D rats were exposed to target concentrations of 0, 1, 5 or 30 mg/m3 of PNP dust via whole body exposure in 1000 L glass and stainless steel chambers. Chamber concentrations were generated via use of a Wright dust feed and determined 3X daily by gravimetric analysis. Particle size determinations were measured weekly. Food and water were available ad libitum at all times other than during exposure. Temperature and humidity, as well as light:dark cycle were controlled. Animals were observed twice daily for mortality and signs of toxicity. Each animal was carfully examined and weighed weekly. Hemoglobin and methemoglobin concentrations were

weighed weekly. Hemoglobin and methemoglobin concentrations were determined by orbital sinus during week 2. Ophthalmic exams were conducted just prior to terminal sacrifice on all animals. The following hematology (RBC, HCT, HGB,PLATELETS, RBC morph, and total and differential leukocyte counts, and clotting time) and blood chemistry (ALT, AST, BUN, TOT BILI, GLU, LD, CHOL, NA, POTAS, CA, CL, PROT, ALBU, GLOB) were evaluated after 4 weeks. No urinalysis was performed. Complete necropsies were conducted on all animals on test. The following organ weights were recorded: lungs, liver, kidneys, brain, heart, adrenals, spleen and testes with epididymides. Thymus wt was not recorded. Histopathological examinations were conducted on approximately 40 tissues and organs, and all gross lesions observed at necropsy, on all high dose and control animals. Clinical pathology, hematology, weekly body weights and weight gains, organ weights and weight ratios of control groups were compared statistically to treated groups of the same sex. Box test was used to determine homogeneity of variances followed by a 1-way classification by ANOVA if variances were homogeneous or use of rank transformation if nonhomogeneous. If found significant ($p<0.05$) Dunnett's t-test was used to compare groups ($p<0.05$).

Result : Mean gravimetric chamber concentrations were 1.09, 5.27, and 29.2 mg/m3. MMD ranged from 5.4 -6.9 u. Prestudy analysis indicated that the PNP dust was homogeneously distributed in the stainless steel chamber. No deaths occurred during the study. Except for dose-related yellow staining attributed to test material, no abnormal physical observations were noted. Ophthalmoscopic e xaminations revealed 11 cases of diffuse anterior capsular cataracts only in HD males and females. Corneal keratitis sicca (inflammation and drying of the cornea and conjuctiva) was noted in 3 HD animals. Periodic changes in body weights were seen inconsistently and in opposite directions for each sex and thus not considered tretment-related. No consistent, dose-related effect was noted in METH values, while some very slight changes in HGB and HCT were seen in HD males. The relationship of these effects to PNP treatment is unclear. No treatment-related effects were seen in other hematologic or clinical chemistry parameters. No gross or microscopic pathological effects or organ weight changes were noted that were attributed to PNP. No effects on the gonads was observed. A NOEL was established as 5 mg/m3.

Test substance : Purity of 99 %.

Reliability : (1) valid without restriction

09.10.2002 (13)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 4 weeks
Frequency of treatment : once daily for the entire test period
Post obs. period : none
Doses : 0, 1, 10, 50, and 100 mg/kg
Control group : yes, concurrent vehicle
NOAEL : >= 50 mg/kg
LOAEL : >= 100 mg/kg
Method : other
Year : 1989
GLP : yes
Test substance : other TS
Method : Groups of 5 male and 5 female S-D rats were administered PNP in distilled water by gavage at doses of 0, 1, 10, 50 and 100 mg/kg at a constant volume of 10 ml/kg. Daily clinical signs were recorded and individual body weights and food consumption were taken weekly for all animals. Hematological (HGB, HCT, RBC, TOT /DIFF LEUKO, MET HGB) and clinical pathological (BUN, GLU, CREAT, ALT, ATS, T PROT, ALBU, GLOB, T BILI, PHOS, NA, K, CL) parameters were measured prior to

GLOB, T BILI, PHOS, NA, K, CL) parameters were measured prior to study termination after 4 weeks. Gross necropsy examinations were conducted at the terminal sacrifice and brain, liver, kidneys, spleen and testes with epididymides were trimmed and weighed. Collected tissues (approx. 40/animal) were preserved and gross lesions, kidneys, livers and spleen were prepared from all animals and examined microscopically. Dosing solutions were analyzed by spectrophotometric means for stablity and concentration.

Result : Analysis of dosing solutions indicated stability and accuracy. One female rat at the 100 mg/kg dose level died shortly after bleeding followed by dosing and is likely treatment-related. Mean body weights and food consumption in treated groups were comparable to control values. No changes were observed in hematology or clinical chemistry values between treated and control groups. No clinical signs of toxicity were observed in survivors. Organ weights, necropsy findings and microscopic examination of treated rats were similar to controls.

Test substance : Purity of 99 %.

Conclusion : This study was a range-find study to set dose levels for study no. HL-88-372. As such, no statistical treatment of data was ascertained.

Reliability : (2) valid with restrictions

09.10.2002 (14)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test

System of testing : Salmonella typhimurium strains TA100, TA98, TA1535 and TA1537

Concentration : 0, 10, 33, 100, 166, 333, 666, 1000 ug/plate

Cycotoxic conc. : 1000 ug/plate (TA100)

Metabolic activation : with and without

Result : negative

Method : OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"

Year : 1983

GLP : yes

Test substance : other TS

Method : Methodology used by NTP based on Ames test plate incorporation assay and consistent with OECD 471. All tests were run in duplicate and three plates were assayed at each dosage for each run both with and without metabolic activation; S9 obtained from male S-D rats injected with Arochlor 1254 (500 mg/ml) five days before they were killed; all tester strains obtained originally from B. Ames; the high dose was designed to produce toxicity (reduced background lawn or solubility limits; sterile DSMO was used as the solvent; negative (solvent) and positive controls (2-aminoanthracene, 4-nitro-o-phenylenediamine, sodium azide and 9-aminoacridine) used were appropriate to detect mutagenicity with or without metabolic activation in each of the 4 tester strains used. A positive response was detected if a reproducible, dose related increase (>2X) was seen in revertant colonies according to a model described by Margolin et al 1981.

Result : No increase in revertants were observed with or without metabolic activation in any of the 4 tester strains.

Test substance : Purity = 99%.

Reliability : (1) valid without restriction
While no statistical methods were used, none were needed to visually inspect and render a conclusion of no increases observed in revertants in any tester strain; further, these findings are consistent with other literature citations using similar methodology

Flag : Critical study for SIDS endpoint

09.10.2002 (8)

Type	:	Chromosomal aberration test
System of testing	:	Chinese Hamster Ovary cell culture
Concentration	:	100 to 2500 ug/ml
Cycotoxic conc.	:	not stated
Metabolic activation	:	with and without
Result	:	positive
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	Study performed under auspices of US NTP program. Doses were based on a preliminary test of cell survival 24 hr after treatment. Cells were collected 10.5 h after treatment by mitotic shaking-off. Slides stained with Giemsa and coded. 100 cells were scored from each of the 3 highest dose groups having sufficient metaphases for analysis (cells with 19-23 metaphases chosen); Positive control groups treated with triethylenemelamine, mitomycin C or Cyclophosphamide), solvent control also used.. Aberrations were typed and recorded separately but analyzed grouped into categories of simple (breaks and terminal deletions), complex (rearrangements and exchanges) and other (i.e pulverized chromosomes). Gaps and endoreduplications were recorded but not included in totals. Aberrations in polyploid cells were not scored. Linear regression of the percentage of cells with aberrations vs. the log-dose was used as the test for trend. A binomial sampling assumption was used and data were analyzed according to the method of Margolin et al Environ Mutag 8:183 (1981). P values were adjusted by Dunnett's method to take multiple dose comparisons into account.
Remark	:	In a concurrent study PNP was negative for SCE induction up to doses that caused severe cell cycle delay (25 ug/ml -S9; 1700 ug/ml +S9).
Result	:	No treatment-related increase in the frequency of structural aberration were noted up to severe cytotoxic levels (>750 ug/ml -S9; Reproducible , dose-related and significant increases in cells with structural chromosomal aberrations were seen at test levels of 1500 to 2000 ug/ml +S9 that induced severe cell cycle delay.
Test substance	:	Purity of 99 %.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

15.10.2002 (4)

5.6 GENETIC TOXICITY 'IN VITRO'

5.7 CARCINOGENITY

5.8 TOXICITY TO REP RODUCTION

Type	:	Two generation study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	F0: males - 113 doses; females - 118 doses; F1: males - 190 doses; females - 180 doses
Frequency of treatment	:	once per day, 5 days per week
Premating exposure period		
Male	:	140 days (100 doses)

Female	:	140 days (100 doses)
Duration of test	:	Through prebreeding, breeding ,gestation, lactation and development through two full generations (1 litter per generation), F2 pups observed through 30 days postweaning.
Doses	:	50, 100, and 250 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	> 250 mg/kg bw
NOAEL F1 Offspr.	:	> 250 mg/kg bw
NOAEL F2 Offspr.	:	> 250 - mg/kg bw
Method	:	other
Year	:	1985
GLP	:	yes
Test substance	:	other TS
Method	:	5-Week old Charles River CD rats began treatment, consisting of 120 female and 60 male rats housed in wire mesh caging. Humidity, temperature and light:dark cycle were controled throughout the study. Water and food were available ad libitum. After random assignment, each of the five test groups began the study (Fo generation) with 24 females and 12 male rats per group. All rats were clipped free of hair along the dorsal body line and reshaved as necessary to allow good dermal contact with the test agent. Dosing periods were lengthened over the periods recommended by EPA guidelines to compensate for a 5-day per week dosing period in this study. Test agents were applied dermally using appropriate-sized syringes, once daily, 5 days /week. Animals were individually weighed at the beginning of each study and dose levels adjusted. F0 animals were treated for the first 140 days of the study (100 applications each). Thereafter, one half of the females in each group were paired with corresponding males until either positive mating was achieved (presence of sperm plug and confirmed by vaginal smear) or it became evident that the pair would not mate. In the latter cases additional cohousing occurred until it became apparent that no further mating would ensue. After successful mating, males and females were separated; F0 males were held until all mating ceased, at which time they were sacrificed and testes, epididymis and skin sections were taken for histopathologic evaluation. Dosing of F0 females continued through the breeding, gestation and lactation periods. Females dosed during gestation were based on the last premating weight. Approximately 21 days after birth, the F1 generation was weaned and F0 females sacrified with their ovaries, uterus and skin sections taken for histopathologic examination. 13 males and 26 females from the F1 generation were randomly selected for continued dosing and breeding in a manner similar to the F0 generation. Application of test materials continued over the next 168 days (120 applications each). Following this period, the F1 rats were mated in a procedure corresponding to the mating of the F0 parental animals. Five males and 5 female pups from the F1 generation were selected at weaning for complete necropsy exam. An additional 5 F2 males and 5 F2 females from each group were randomly selected and retained in wire cages for 30 days after weaning. Dosing of all F1 rats continued throughout breeding, gestation, lacatation and until 30 days after all F2 rats had been weaned. Thereafter, all F1 rats and remaining F2 rats were submitted for complete necropsy. All animals dying spontaneously during the course of the study were submitted for necropsy. All rats which underwent necropsy were subjected to histopathological assessment of the following tissues and organs: (brain, spinal cord, eye, salivary gland, heart, thymus, thyroid, lungs, bronchi, esophagus, stomach, small intestine, large intestine, pancreas, adrenal glands, kidneys, liver, testes, epididymis, urinary bladder, male accessary glands, ovaries, corpus uteri, cervix uteri, spleen, lymph nodes, sernum, femur, skeletal muscle, mammary gland, treated skin and untreated skin. Organ weights were recorded for scheduled sacrifies from F1 and F2 animals: liver, kidneys, heart, gonads (F0 males also), and brain. Observations for toxic signs, breeding and nesting behavior were recorded daily for all animals. Weights of all dosed rats were recorded weekly. Breeding and litter observations included: litter size, individual pup weights

Breeding and litter observations included: litter size, individual pup weights and viability at birth and on days 4, 7, 14, and at weaning. The following indices were calculated to assess reproductive success: fertility (no. of pregnancies/no. mated) gestation (% of pregnancies resulting in birth of live litters), viability (pups surviving at least to day 4 of life) and lactation (pups surviving at least to day 21 of life). Group-wise statistical ($p < 0.05$) comparisons were made of body weights, absolute and relative organ weights.
The High dose (250 mg/kg/d) was selected based on a range-find study indicating this level to be 1/4 LD50 dermally, and would allow sufficient survival; both an ethanol vehicle (used at 500 mg/ml) control group (0.5 ml/kg/d) and a saline control group (0.5 ml/kg/d) were also evaluated concomittantly. Multigeneration study methodology was modified (dosing took place 5 d/wk rather than 7 d/wk) from test guidelines recommended in TFX Collins Handbook on Teratology, Vol. IV, Chapter 7: Multigeneration Reproduction Studies. 1978.

Result : All F0 and F1 rats dosed dermally with PNP or ethanol exhibited a pattern of dermal irritation consisting of varying degrees of erythema, scaling, scabbing and cracking ; some degree of dose-response was noted in PNP-treated groups. No treatment-related mortality was observed in either the F0 or F1 parental generation, and no effects of treatment were noted in body weights in these groups. No evidence of effects in mating, pregnancy, behavior,and growth were found in parents or subsequent F1 and F2 generations.All group-wise comparison of organ weights, including gonads, were unremarkable. No evidence of histopathologic alterations was seen in any tissue examined, including the gonads.

Test substance : Purity of test substance used - 99.1%

Reliability : (1) valid without restriction
Study sufficiently adequate to be accepted to fulfill US EPA pesticide reregistration requirement for reproductive toxicity endpoint.

23.08.2002 (1)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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(14) Solutia study no. HL-88-347. 4-Week Dose Range-Finding Study in Rats with p-Nitrophenol. [EPA no. 86-890000362]

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7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT